BOOK REVIEW

Antibiotics: Actions, origins, resistance, by C. Walsh. 2003. Washington, DC: ASM Press. 345 pp. $99.95 (hardcover).

Many of us value Chris Walsh's *Enzymatic Reaction Mechanisms* (Walsh 1998), a textbook and monograph that has its solid place on the protein chemist's shelf. In the last decade, his group at Harvard has contributed landmark papers both on antibiotic biosynthesis and resistance mechanisms, and from his protein structural background Walsh has now again set a new standard with his *Antibiotics: Actions, Origins, Resistance* in the current state of antibacterial research. This is obvious as we compare his new book to the now outdated 1995 revised edition of *Antibiotics: A Multidisciplinary Approach* (278 pages) by Giancarlo Lancini, Francesco Parenti, and Gian Gualberto Gallo (Lancini et al. 1995); the 1992 encyclopedic *Biochemie der Antibiotika* by Udo Gräfe (almost 600 pages with more than 2000 references) (Gräfe 1992); the basic textbook *Bacteria Versus Antibacterial Agents: An Integrated Approach* by Oreste A. Mascaretti (420 pages) (Mascaretti 2003); or the 2nd edition of Pratt's *Antimicrobial Drugs* edited by Eric M. Scholar and William B. Pratt (Scholar and Pratt 2000), providing an extensive approach from the drug perspective (more than 600 pages). No author has yet dealt in such depth with the molecular basis of actions and generation of these remarkable metabolites. This volume of 345 pages with approximately 500 references is an advanced textbook with a perspective focusing on targets, resistance, and biosynthesis.

Why do we need such an approach? This has been stated in the Introduction: "The inevitable progression of bacteria exposed to antibiotics to develop resistance ensures the need for continual cycles of discovery and development of new antibiotics." We are "not in a 'post-antibiotic' era; hopefully we are entering a new era of much greater awareness of the precious nature of effective antibiotics," as David Hopwood has commented (Hopwood 2003). We are currently facing a growing number of infections, and a growing number of patients who are dying from infectious diseases. At the same time, the number of reports on drug-resistant strains of bacteria is rising, while industrial efforts in antibiotic discovery and development have been declining (Hughes 2003; Fraser 2004). But there is no chance to escape the many actions of our successful fellow prokaryotes. It is inevitable that we evaluate bacterial pathogens' genomes for essential genes and develop new antibiotics, in addition to the improvement of surveillance and health infrastructure measurements. This book provides a solid and up-to-date background for such efforts.

The text is divided into four sections: targets, resistance, biosynthesis, and strategies. In an introductory chapter, basic concepts of antibiotic discovery, structural classes and targets, self-protection, and the emergence and challenge of resistance are neatly presented. In the target section, the main topic is cell wall biosynthesis, followed by bacterial translation, replication, and folate metabolism. The cell wall chapter deals in detail with the phases of peptidoglycan assembly, introducing, among others, bacitracin, ramoplanin, and mersacidin, followed by transpeptidation inhibition with the development of generations of β-lactams and the introduction of glycopeptides of the vancomycin type, and finally transglycosylase inhibition by moenomycin. The protein synthesis part illustrates well basic concepts using recently established protein–nucleic acid structures of the prokaryotic ribosome with the binding of erythromycin and related macrolides to the polypeptide exit tunnel, puromycin and others at the peptidyltransferase center, and tetracyclins and aminoglycosides on the 16S rRNA. The replication chapter focuses on DNA gyrase (topoisomerase II) and the quinolones. Rifamycins are treated among sulfa drugs and nonribosomally and ribosomally formed peptides in a final chapter.

In the resistance section, the main intrinsic mechanisms of antibiotic modification, efflux, and target alteration are presented. The introductory chapter outlines the emergence of resistant bacteria and self-protection mechanisms, including export by an ABC transporter (lantibiotics, macrolides), formation of inactive precursors (oleandomycin and mitomycin), methylation of the target 23S rRNA glycosylation (erythromycin), mutational alteration (DNA gyrase and aminocoumarins), and structural alteration of the target peptidolglycan precursor (vancomycins). The chapter on modification and destruction of antibiotics focuses on the various classes of β-lactamases, their inhibitors, and especially mechanisms of their induction. This is followed by a summary chapter on efflux pumps, linking the known superfamilies to bacterial protein secretion. The final chapter covering target alterations includes, besides the incompletely understood β-lactam-binding proteins, the murein alteration system, which was largely uncovered in the Walsh lab.

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The biosynthesis section, which definitely is unusual in this context, reflects the current major interests of the Harvard group. Why then should we be aware of complex processes like polyketide and nonribosomal peptide formation? Understanding the continuous system of microbial survival at the interface of chemical communication based on the production of antibiotics with the corresponding resistance will surely help us to manage our survival as part of it. The flexible systems of biosynthesis and resistance are frequently linked sets of genes that are subject to horizontal transfer events causing extensive genomic alterations. The production of antibiotics and similar nonantibacterial compounds represents a major pathogenicity factor in many systems. And finally, antibiotic biosynthesis as a flexible system is especially intriguing as its understanding may lead us to an accelerated creation of new drugs (Walsh 2004). The introductory chapter presents the known regulatory mechanisms for the expression of biosynthetic genes mainly in Streptomycetes. This is followed by two chapters explaining the assembly-line enzymology of polyketide and nonribosomal peptide formation. The final chapter provides examples of the complex enzymology of other systems, including fosfomycin, streptomycin, aminocoumarins, and chloramphenicol, and the ribosomally made lantibiotic microcin.

The last section presents a survey of current strategies to fight the problems of infectious diseases, and many of those are relevant for drug discovery in general. Clearly, genomic data provide new targets, including the expression of essential genes of the pathogens. A more detailed understanding of crucial prokaryotic processes especially from their protein structural background including cell wall formation, replication, translation, lipid biosynthesis, and an emerging field, interbacterial communication, is the logical continuation of ongoing work. A small chapter outlines combinatorial approaches for the creation of new molecules, and the final chapter summarizes the problems of the current state of antibiotic uses. This chapter is of special importance and perhaps should be consulted first. Changing patterns of infectious diseases, emerging new pathogens, and misuse of antibiotics are the main themes, which call for the improvement of monitoring and improved public health infrastructures worldwide.

Chris Walsh has assembled here the essential background for the field of antibacterials, suitable as an advanced textbook and reference source for those working in the field.

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